

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Docket No: A8275

Johnson CHUNG, et al.

Appln. No.: 10/057,561

Group Art Unit: 1651

Confirmation No.: 4657

Examiner: LILLING, H. J.

Filed: January 29, 2002

For: MUTANT ACTINOSYNNEMA PRETIOSUM STRAIN WITH INCREASED
MAYTANSINOID PRODUCTION

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Graham Sidney Byng (full name), hereby declare and state:

THAT I am a citizen of United Kingdom (country);

THAT I have received the degree of Ph.D.(degree) in 1977 (year) from Liverpool

University England (institution);

THAT I have been employed by MDS Pharma Services (formerly Panlabs) since 1990
(year), where I hold a position as Vice President and General Manager(job title), with
responsibility for Strain Improvement and Fermentation Development (brief description of
responsibilities).

The above-referenced U.S. patent application includes methods that may be used to
prepare and isolate microorganisms of the genus *Actinosynnema* that produce increased amounts
of maytansinoids, including ansamitocins such as ansamitocin P-3, as compared to a parent



strain. As explained in detail in the specification, the methods involve isolating *Actinosynnema* strains that exhibit fermentative production of maytansinoids on media containing appropriate carbon sources, subjecting strains to mutagenesis, re-isolation of individual colonies that grow on the selected media, further mutagenesis and further isolation. The levels of maytansinoids produced by isolated colonies are then determined.

The methods described in the specification are easily conducted by one with basic laboratory skills. Indeed, the skilled artisan would readily recognize that practice of the method would be well within the purview of the average laboratory technician.

Furthermore, colonies exhibiting increased ansamitocin production are easily produced. Indeed, the experimental procedure described in the specification has been conducted over 100 times. As a result of the repeated use of the experimental procedure, over 3000 strains of *Actinosynnema* have been isolated that produce increased ansamitocin production. Thus, it is evident that the skilled artisan would readily expect that mutant strains that produce increased levels of ansamitocin could be easily isolated.

Given the similarities known to exist between species within the genus *Actinosynnema*, the skilled artisan would expect that the methods taught in the specification could be used to easily produce variant strains exhibiting increased ansamitocin production for all members of the genus.

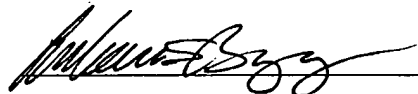
I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States

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Code, and that such willful false statements may jeopardize the validity of the application or any
patent issuing thereon.

Date: Nov 26 2003

A handwritten signature in black ink, appearing to be "M. M. F. S. S.", written over a horizontal line.

Graham Byng Ph.D.

Vice President and General Manager, Fermentation Technologies

e-mail: graham.byng@mdsps.com

Dr. Byng joined MDS Pharma Services in 1990. He is responsible for the Fermentation Technologies business operated out of the Taiwan facility.

Dr Byng has more than 20 years of industrial microbiology experience in the pharmaceutical industry, including 7 years at Miles Inc.. His key areas of expertise include classical yield improvement, microbial isolation, natural product chemistry, fermentation and process development, molecular biology as applied to pathway engineering and protein production, biocatalysis, dairy microbiology, carbohydrate polymers and food additives

Dr Byng holds a Ph.D. and B.Sc. in biochemistry from Liverpool University, England. He conducted postdoctoral research at the State University of New York, Binghamton, NY. A frequent lecturer at scientific meetings, he also has published over 20 journal articles and has 16 patents and applications. Dr. Byng is a member of the American Society of Microbiology, Society for Industrial Microbiology and the American Chemical Society

Pertinent publications and presentations relating to strain improvement are as follows:

Publications

22. Vinci, V.I. and G.S. Byng, 1999. Strain improvement by non-recombinant methods. *Manual of Industrial Microbiology and Biotechnology*. 2nd Ed. Eds. A.L. Demain and J.E. Davies
21. Byng, G.S. 1998. Strain improvement in the modern fermentation industry. *Pharmaceutical Manufacturing International*. P. 9, Sterling Publications Ltd., London

Presentations

- 38 Desai R.P., T. Leaf, Z. Hu, C.R. Hutchinson, J. Galazzo, P. Licari, A. Hong and G.S. Byng 2003 Combining classical and rational strategies for improved production of erythromycin aglycone analogs (Recent Advances in Fermentation Technology, St Petersburg FL.)
36. Byng, G.S. 2000 Strain improvement for fermentation derived products (Chemical and Pharmaceutical Ingredients Meeting, Milan Italy)

- 31 Byng, G.S., C.Thornton and A. Hong 1998. Impact of classical strain improvement on media optimization and fermentation process development. (All India Biotech Assoc. New Delhi India.).